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EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 09/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/723,681	ROTH ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6-8,18-20,53-57,61,62 and 67-69* is/are pending in the application.

4a) Of the above claim(s) *56 and 57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6-8,18-20,53-55,61,62 and 67-69* is/are rejected.

7)☒ Claim(s) *18, 54, 62, 69* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/2006, 9/2005*.
4) ☒ Interview Summary (PTO-413) (2) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group 1, in the reply filed on 6/19/2006, as well as election of a polymorphism at position 36424 in SEQ ID NO: 2 by telephone on 7/11/2006 is acknowledged (the election of a specific polymorphism in SEQ ID NO: 2 in the reply filed 6/19/2006 did not correspond to the positions set forth in the claims and appeared to be in error). The traversal is on the ground(s) that claim 20 should be in group I. This is found persuasive as claim 20 was mistakenly placed in group II. The traversal further asserts that a) claims 56 and 57 should be included in Group 1 as there is no undue search burden because search for claims 1 and 53 will pertain to the search for subject matter of claims 56 and 57 and b) that the election of the polymorphisms should not be a requirement for restriction but instead a species election. These arguments have been thoroughly reviewed but were not found persuasive. Searching the art for breast cancer preventative procedures such as selective hormone receptor modulators will not provide art relating to breast cancer detection procedures such as biopsy procedure. These are entirely different procedures which require different steps and are not obvious over each other. The methods steps of claim 53 require administering one or the other. Accordingly, the method of detection and the method of prevention are patentably distinct and constitute a search burden. Claims are required to be searched not only for art purposes for patentability under 35 USC 102 and 103, but also under 35 USC 112, first paragraph. The search for breast cancer preventative procedure in claim 53 encompassing the myriad of breast cancer preventative procedures listed in claims 56 and 57 represent a serious search burden on the office. With regard to the restriction between the polymorphisms as recited in claim 1, it is noted that claim 1,

directed to SEQ ID NO: 2, is linking with regard to the polymorphisms listed in claim 6, for example. The restriction requirement and how it affects the examination of claim 1, for example, is set forth below.

Claims 1, 2, 19, 20, 53, in part directed to detection, 55, 61, and 67-68 link(s) the polymorphisms in claims 6-7, 18, 54, 62 and 69. The restriction requirement among the linked inventions is subject to the nonallowance of the linking claim(s), claims 1, 2, 19, 20, 53 directed to detection, 55, 61, and 67-68. Upon the indication of allowability of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise requiring all the limitations of the allowable linking claim(s) will be rejoined and fully examined for patentability in accordance with 37 CFR 1.104. Claims that require all the limitations of an allowable linking claim will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312. Applicant(s) are advised that if any claim(s) including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. In re Ziegler, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

The traversal that the restriction requirement between polymorphisms should be an election of species has been thoroughly reviewed but was not found persuasive as the nucleic

acid molecules comprising each polymorphism are structurally and functionally distinct. A search for each polymorphism is not coextensive. Searching must be conducted not only in sequence databases such as Genbank, but in the patent and non patent literature as well as polymorphism databases such as dbSNP because sequence databases, such as Genbank, do not normally provide information on SNPs. The position of each SNP in the chromosome does not decrease the search burden as polymorphisms are not usually referenced in journal articles with regard to the position on the chromosome. A complete search for each polymorphism is not coextensive. Search and examination of more than one of the polymorphisms for patentability presents a serious burden on the office. The response's assertion that the claimed polymorphisms are all associated with breast cancer is not found persuasive. As can be seen in table 19, the majority of the claimed polymorphisms are not significantly associated with breast cancer ($p > .05$). The polymorphisms are structurally and functionally distinct.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 56 and 57 are withdrawn from consideration as being drawn to non elected inventions.

Specification

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Information Disclosure Statement

4. The information disclosure statement filed 7/6/2006 listing pending applications fails to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement. The information disclosure statement has been placed in the application file, but the information referred to therein has not been considered. See MPEP 609.04 (a) (II). The IDS fails to comply with section 4 in relation to the pending applications for section 1 above.

"Pending U.S. applications that are being cited can be listed under the non-patent literature section or in a new section appropriately labeled. The list of information complying with the *format requirements of 37 CFR 1.98(a)(1)* and the identification requirements of 37 CFR 1.98(b) may not be incorporated into the specification of the application in which it is being supplied, but must be submitted in a separate paper."

5. The information disclosure statement filed in form PTO/SB/08a on 7/6/2006 has been considered.

Claim Objections

6. Claims 18, 54, 62, and 69 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim can only refer to claims in the alternative. See MPEP § 608.01(n).

7. Claim 54 is objected to for minor informalities. The claims recite the phrase "wherein the one or more polymorphic variations are detected at one or more positions in" twice. Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-2, 6-8, 18-20, 53-55, 61-62 and 67-69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to identifying any subject at risk of breast cancer or detecting breast cancer, or selecting any subject that will respond to a treatment of breast cancer which comprises detecting the presence or absence of one or more polymorphic variations in a) SEQ ID NO: 2, b) a nucleotide sequence which encodes a polypeptide encoded by SEQ ID NO: 2, c) a nucleotide sequence which encodes a polypeptide that is 90% or more identical to the

amino acid sequence encoded by SEQ ID NO: 2, or d) any fragment of a, b, or c; whereby the presence of the polymorphism is indicative of the subject being at risk of breast cancer, or administering a breast cancer detection procedure based on the presence or absence of the one or more polymorphisms, or selecting a subject that will respond to the breast cancer treatment based upon the presence or absence of the one or more polymorphic variations. The claims are also broadly drawn to detecting one or more polymorphic variations in linkage disequilibrium with the polymorphism at position 36424 of SEQ ID NO:1.

The claims (eg: 67) are also drawn to determining a risk of breast cancer in a subject which comprises detecting the presence or absence of two or more polymorphic variations in a nucleotide sequence (claim 68 is further drawn to detecting them in two or more sequences) selected from: a) SEQ ID NO: 2, b) a nucleotide sequence which encodes a polypeptide encoded by SEQ ID NO: 2, c) a nucleotide sequence which encodes a polypeptide that is 90% or more identical to the amino acid sequence encoded by SEQ ID NO: 2, or d) any fragment of a, b, or c; whereby the presence of the polymorphic variation is indicative of the subject being at risk of breast cancer.

The genus encompassed by the claims is a broad variable genus as discussed below. The claims encompass not only detection of any polymorphism in SEQ ID NO: 2, which the specification teaches is a nucleotide sequence of a MAPK10 "region", but in sequences which encode a polypeptide encoded by SEQ ID NO: 2, sequences which encode a polypeptide with 90% identity to a polypeptide encoded by SEQ ID NO: 2, as well as sequences comprising fragments of such. The claims therefore encompass detection of polymorphisms in a large genus of variants, mutants and homologs of SEQ ID NO: 2, from any source. However, the

specification does not teach degenerate variants of SEQ ID NO: 2, nor does the specification teach any homologs of SEQ ID NO: 2 which encode a polypeptide with 90% identity with a polypeptide encoded by SEQ ID NO: 2. The specification does not teach any polymorphisms whatsoever, in any variants, mutants or homologs encompassed by sections b-d of claims 1, 53, 61, and 67, or any polymorphisms in any other species, let alone any SNPs that are statistically associated with breast cancer. The claims also broadly encompass identifying SNPs in any subject, which encompasses any species, however the specification only teaches the identification of 17 particular statistically associated polymorphisms in SEQ ID NO: 2 in humans (table 19) which is over 76 kb.

The broad genus further encompasses detecting polymorphic variations that are in linkage disequilibrium with the elected polymorphic variation at position 36424 of SEQ ID NO: 2. At page 4, in the legend to figure 15, the specification provides that polymorphic variations in certain regions in SEQ ID NO: 2 that "are in linkage disequilibrium". For example, the specification teaches that polymorphic variations in the region spanning positions 23826-36424, 46176-65527, 4512-8467 or 13787-14355 are in linkage disequilibrium. However, at table 19, a large number of polymorphic variations within these regions do not appear to be statistically associated with breast cancer. Additionally, at figure 15, the specification teaches only "12/65 SNPS significant at alpha =0.01". While the SNP at position 36424 has a p value of 0.029, the SNP at position 35999 of SEQ ID NO: 2 has a p value of 0.596, which does not appear significant. Accordingly, the detection of a SNP within this region would not be predictably diagnostic of breast cancer or risk of breast cancer, let alone therapeutic response, to which the specification is silent. It is clear from table 19, that a SNP, by virtue of being in the MAPK10

"region" or a region spanning that noted at page 4, is not necessarily associated with breast cancer. The specification provides no structure/function correlation between any particular SNP in linkage disequilibrium with the elected SNP that is diagnostic for breast cancer risk, detection, or response to therapy. With regard to claims 67-68, which encompasses detecting two or more nucleotide sequences, the specification does not teach the genetic background in which the alleles of SNPS in table 19 are found. Accordingly, it is unclear as to what other sequences are associated with the SNPs set forth in table 19 for SEQ ID NO: 2, or any other SNPs in the large genus of mutants, variants, and homologs encompassed by the claims.

The broad genus also encompasses (claims 61-62) selecting a subject that will respond to treatment of breast cancer based on the presence or absence of any SNP in the broadly claimed regions noted above, as well as the elected SNP. However the specification provides no teaching or guidance whatsoever as to whether any of the identified SNPs, including the C variation at position 36424 of SEQ ID NO:1 are predictive of a subject's response to treatment. It is not known if the C at position 36424 of SEQ ID NO: 2 is indicative of a subject responding or not responding to treatment or whether the variant is indicative of response to certain types of treatment, for example a particular chemotherapeutic drug, but not others. The specification provides absolutely no guidance as to whether any of the disclosed SNPs or broadly encompassed SNPs affect the function of the gene in any way to predict a subject's response to treatment.

The current claims encompass detection in a large variable genus of nucleic acids which comprise polymorphisms in any region of the MAPK10 gene, surrounding region, or homolog from any source. The genus includes an enormous number of polymorphisms and mutations for

which no written description is provided in the specification. The specification only teaches of 17 particular polymorphisms for which data is provided (eg: T/C at position 36424 of SEQ ID NO: 2). With regard to the elected position, the specification teaches that a T at position 36424 of SEQ ID NO: 2 was statistically associated (p=0.0070) with breast cancer (table 6B). Thus, applicant has express possession of only 17 particular polymorphisms in SEQ ID NO: 2 which are associated with breast cancer, in a genus which comprises hundreds of millions of different possibilities.

The broad variable genus is not represented by the particularly 17 named variants in table 19 of the specification for the reasons which follow. In the broadly claimed invention, no common element or attributes of the sequences are disclosed which would permit selection of sequences as polymorphisms. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations of associating a polymorphism with breast cancer or therapeutic response is provided. However, no predictable correlation between the structural alterations of the 17 polymorphisms disclosed and breast cancer is provided by the specification. The specification does not teach the function of polymorphisms of the MAPK10 "region" nor how their function, or lack of function, or altered function are predictably associated with breast cancer or therapeutic response. The specification teaches 68 SNPs (table 19) were found in SEQ ID NO: 2, but that only 17 particular polymorphisms exhibited a p value of less than 0.05. Thus it is clear that "any" polymorphism in the encompassed nucleic acids would not be predictable of breast cancer association or treatment. It is further noted that the claims (6, 7, 54, 62, 69) broadly encompass "any" polymorphic variation at the disclosed position (eg, elected position 36424 of SEQ ID NO: 2),

but only teaches 2 out of 4 possible variations at each position (T/C at position 36424). The specification does not teach if a G or an A would be statistically associated with breast cancer or treatment nor does it provide any guidance as to whether the particular nucleotide variant even exists. The specification provides no guidance that any alteration, in any MAPK10 gene, in any subject, is diagnostic for increased risk for breast cancer or predictive of therapeutic response. With regard to claims 61-62, the specification provides no teaching or guidance as to whether any SNP in the broadly encompassed sequences has any predictable response to therapy.

Further, these claims expressly encompass allelic variants including insertions, deletions, substitutions and transversions at thousands of different sites. No written description of alleles, of upstream or downstream regions containing additional sequence, which are associated with any phenotype are described in the specification. Additionally, the specification provides no evidence that any SNP at such position, in either humans, or mice or dogs for example, provides a predictable association with breast cancer or predictive of therapeutic response. The polymorphisms shown are not representative of the genus of any polymorphism associated with breast cancer because it is not clear which polymorphisms within a MAPK10 region would have the same affect. It is not clear whether the polymorphisms shown are causative for the detected phenotype or whether they may simply represent markers for another gene that is in linkage disequilibrium with the specific alleles at issue, and the actual gene which is involved in the breast cancer may be tens of thousands of nucleotides distant from the polymorphisms described in the specification. The specification provides no guidance that the specific alleles exist in other species, therefore, there is no teaching or guidance as to the identity of alleles in linkage disequilibrium with recited alleles in other species. The specification fails to provide any

teaching or guidance as to what the structure of phenotypically associated alleles would be in variants or homologs of SEQ ID NO: 2 in humans, or in MAPK10 or variants or homologs in other species. Accordingly, the 17 particularly disclosed variants are not representative of the large variable genus encompassed by the claimed invention.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) In the instant case, the specification fails to teach the necessary common attributes or features of the genus of encompassed nucleic acids and polymorphisms in view of the species disclosed. The skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. As such, one of skill in the art would not recognize that applicant was in possession of the genus of nucleic acids and polymorphisms encompassed by the broadly claimed invention. However, Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in

possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

10. Claims 1-2, 6-8, 18-20, 53-55, 61-62 and 67-69 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying a human subject at risk of breast cancer comprising a) detecting the presence of a C at nucleotide position 36424 of SEQ ID NO: 2 and b) identifying the human subject as having an increased risk of breast cancer or administering a breast cancer detection procedure, does not reasonably provide enablement for identifying a subject at risk of breast cancer or detecting breast cancer, or selecting a subject that will respond to a treatment of breast cancer which comprises detecting the presence or absence of one or more or two or more polymorphic variations in a) SEQ ID NO: 2, b) a nucleotide sequence which encodes a polypeptide encoded by SEQ ID NO: 2, c) a nucleotide sequence which encodes a polypeptide that is 90% or more identical to the amino acid sequence encoded by SEQ ID NO: 2, or d) any fragment of a, b, or c; or in two or more nucleotide sequences, whereby the presence of the polymorphism is indicative of the subject being at risk of breast cancer, or administering a breast cancer detection procedure based on the presence or absence of the one or more polymorphisms, or selecting a subject that will respond to the breast cancer treatment based upon the presence or absence of the one or more polymorphic variations. The claims are also limited to detecting one or more polymorphic variations in linkage disequilibrium with the polymorphism at position 36424 of SEQ ID NO:1.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claims are broadly drawn to identifying any subject at risk of breast cancer or detecting breast cancer, or selecting any subject that will respond to a treatment of breast cancer which comprises detecting the presence or absence of one or more polymorphic variations in a) SEQ ID NO: 2, b) a nucleotide sequence which encodes a polypeptide encoded by SEQ ID NO: 2, c) a nucleotide sequence which encodes a polypeptide that is 90% or more identical to the amino acid sequence encoded by SEQ ID NO: 2, or d) any fragment of a, b, or c; whereby the presence of the polymorphism is indicative of the subject being at risk of breast cancer, or administering a breast cancer detection procedure based on the presence or absence of the one or more polymorphisms, or selecting a subject that will respond to the breast cancer treatment based upon the presence or absence of the one or more polymorphic variations. The claims are also broadly drawn to detecting one or more polymorphic variations in linkage disequilibrium with

the polymorphism at position 36424 of SEQ ID NO:1. The claims (eg: 67) are also drawn to determining a risk of breast cancer in a subject which comprises detecting the presence or absence of two or more polymorphic variations in a nucleotide sequence (claim 68 is further drawn to detecting them in two or more sequences) selected from: a) SEQ ID NO: 2, b) a nucleotide sequence which encodes a polypeptide encoded by SEQ ID NO: 2, c) a nucleotide sequence which encodes a polypeptide that is 90% or more identical to the amino acid sequence encoded by SEQ ID NO: 2, or d) any fragment of a, b, or c; whereby the presence of the polymorphic variation is indicative of the subject being at risk of breast cancer.

The nature of the claimed invention, therefore, requires the knowledge of predictive associations between any polymorphism in any of the recited nucleic acids, or any polymorphism in linkage disequilibrium with such, in any subject and a risk for breast cancer or therapeutic response to breast cancer treatment.

The amount of direction or guidance and presence/absence of working examples:

The specification teaches that SEQ ID NO: 2 is a nucleotide sequence of a MAPK10 "region" (page 3). However, the specification does not teach which portions of SEQ ID NO: 2 are directed to the human MAPK10 gene, where the regulatory regions, such as the promoter, lie, and whether the sequence comprises the entire gene. The specification teaches that a number of polymorphisms were identified in the sequence and teaches that a C variation at position 36424 of SEQ ID NO: 2 is statistically associated with breast cancer ($p=0.0070$; see page 78, table 6B). The specification teaches that a number of SNPs were identified in females with breast cancer (cases) and females without cancer (controls) and that SNPs were considered as being associated

with breast cancer if the allele frequency between cases and controls was statistically significant (page 74, para 0247). The specification teaches 68 SNPs in the "MAPK10 proximal region" were found (page 96, table 19), but only 17 have p values of less than 0.05.

However, the claims broadly encompass detection in variants, mutants and homologs of SEQ ID NO: 2 (sections b-d of claim 1, for example), and the specification does not teach whether any SNPs are statistically associated with breast cancer in such sequences. The claims are drawn not only to detection of any polymorphism in SEQ ID NO: 2, but in sequences which encode a polypeptide encoded by SEQ ID NO: 2, sequences which encode a polypeptide with 90% identity to a polypeptide encoded by SEQ ID NO: 2, as well as sequences comprising fragments of such. The claims therefore encompass detection of polymorphisms in a large genus of variants, mutants and homologs of SEQ ID NO: 2, from any source. However, the specification does not teach degenerate variants of SEQ ID NO: 2, nor does the specification teach any homologs of SEQ ID NO: 2 which encode a polypeptide with 90% identity with a polypeptide encoded by SEQ ID NO: 2. The specification does not teach any polymorphisms whatsoever, in any of the sequences encompassed by sections b-d of claims 1, 53, 61, and 67, or any polymorphisms in any other species. The claims also broadly encompass identifying SNPs in any subject, which encompasses any species, however the specification only teaches the identification of 17 particular statistically associated polymorphisms in SEQ ID NO: 2 in humans.

The claims further encompasses detecting polymorphic variations that are in linkage disequilibrium with the elected polymorphic variation at position 36424 of SEQ ID NO: 2. At page 4, in the legend to figure 15, the specification provides that polymorphic variations in

certain regions in SEQ ID NO: 2 that "are in linkage disequilibrium". For example, the specification teaches that polymorphic variations in the region spanning positions 23826-36424, 46176-65527, 4512-8467 or 13787-14355 are in linkage disequilibrium. However, at table 19, a large number of polymorphic variations within these regions do not appear to be statistically associated with breast cancer. Additionally, at figure 15, the specification teaches only "12/65 SNPS significant at alpha =0.01". While the SNP at position 36424 has a p value of 0.029, the SNP at position 35999 of SEQ ID NO: 2 has a p value of 0.596, which does not appear significant. Accordingly, the detection of a SNP within this region would not be predictably diagnostic of breast cancer or risk of breast cancer, let alone therapeutic response, to which the specification is silent. It is clear from table 19, that a SNP, by virtue of being in the MAPK10 "region" or a region spanning that noted at page 4, is not necessarily associated with breast cancer. The specification provides no predictable correlation between any particular SNP in linkage disequilibrium with the elected SNP that is diagnostic for breast cancer risk, detection, or response to therapy.

Further, claims 61-62 are specifically drawn to selecting a subject that will respond to treatment of breast cancer based on the presence or absence of any SNP in the broadly claimed regions noted above, as well as the elected SNP. However the specification provides no teaching or guidance whatsoever as to whether any of the identified SNPs, including the C variation at position 36424 of SEQ ID NO:1 are predictive of a subject's response to treatment. It is not known if the C at position 36424 of SEQ ID NO: 2 is indicative of a subject responding or not responding to treatment or whether the variant is indicative of response to certain types of treatment, for example a particular chemotherapeutic drug, but not others. The specification

provides absolutely no guidance as to whether any of the disclosed SNPs or broadly encompassed SNPs affect the function of the gene in any way to predict a subject's response to treatment.

With regard to claims 67-68, which encompasses detecting two or more nucleotide sequences, the specification does not teach the genetic background in which the alleles of SNPS in table 19 are found. The skilled artisan would be unable to predict what other sequences are diagnostic of breast cancer risk and associated with the SNPs set forth in table 19 for SEQ ID NO: 2, or any other SNPs in the mutants, variants, and homologs encompassed by the claims.

The specification provides no universal correlation that any SNP in any of the claimed nucleic acids would be associated with breast cancer or response to treatment nor does it provide any way to predict which sequences within the broadly claimed sequences would be "breast cancer associated". Of 68 disclosed SNPs, the specification teaches a statistically significant association between only 17 SNPs and breast cancer, and does not teach any SNP which is predictive of response to treatment. Thus it is clear that "any" polymorphism in the encompassed nucleic acids would not be predictable of breast cancer association or treatment. It is further noted that the claims broadly encompass "any" polymorphic variation at the disclosed position (eg, elected position 36424 of SEQ ID NO: 2), but only teaches 2 out of 4 possible variations at each position (T/C at position 36424). The specification does not teach if a G or an A would be statistically associated with breast cancer or treatment nor does it provide any guidance as to whether these particular nucleotide variants even exist.

Additionally, the specification provides no guidance as to how the SNP at 36424 (C), or any of the other 16 statistically significant variants, function to provide for increased risk of

breast cancer. The specification provides no structure/function correlation between the disclosed SNPs and breast cancer for the skilled artisan to be able to predict which other positions within the claimed sequences might be predictably associated with the claimed phenotypes. It is not clear if any other variant at that position would have the same effect.

It is not known whether this polymorphism exists in other variants or homologs or other mammalian genes or what other variant positions would be in another gene or whether a polymorphism would have the same effect in another gene, or what the identity of that polymorphism might be. Therefore, the skilled artisan would be unable to predictably correlate any other structural change in any other region of MAPK10 in any other species. The elected allele could be part of a breast cancer-associated haplotype, however the causative mutation is not necessarily one of the SNPs taught in the specification. The causative mutation could be in a gene thousands of nucleotides away, however the specification provides no indication of what this allele might be.

The specification provides no predictable association that any alteration, in any MAPK10 gene, in any subject, is diagnostic for increased risk of breast cancer or therapeutic response. No common element or attributes of the sequences are disclosed which would permit selection of sequence polymorphisms as diagnostic for an increased risk of breast cancer or predictive of therapeutic response. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations of associating a polymorphism with breast cancer or therapeutic response is provided. Further, these claims expressly encompass allelic variants including insertions, deletions, substitutions and transversions at thousands of different sites. However, the specification provides no evidence

that any polymorphic variation at such positions, in either humans, or mice or dogs for example, provides a predictable association with breast cancer or therapeutic response. The polymorphisms shown are not predictive of the genus of any polymorphism associated with breast cancer because it is not clear which polymorphisms within "any" MAPK10 sequence would have the same affect. It is not clear whether the polymorphisms shown are causative for the detected phenotype or whether they may simply represent markers for another gene that is in linkage disequilibrium with the specific alleles at issue, and the actual gene which is involved in the detected breast cancer association may be tens of thousands of nucleotides distant from the polymorphisms described in the specification. The specification does not teach the function of polymorphisms of SEQ ID NO: 2, nor how their function, or lack of function, or altered function are predictably associated with breast cancer or therapeutic response.

The state of the prior art and the predictability or unpredictability of the art:

At the time the invention was filed, the prior did not teach the function or biological activity of mutations in MAPK10 with regard to breast cancer or therapeutic response. The specification demonstrates the unpredictability of this invention since 51 out of 68 of the identified SNPs in SEQ ID NO: 2 were not statistically significant and do not appear to be breast cancer associated given the data in the specification. Thisted et al (see galston.uchicago.edu/~thisted/, pages 1-5) notes that "It has become scientific convention to say that p-values exceeding .05 (one in twenty) just aren't strong enough to be the sole evidence that two treatments being studied really differ in their effect (see page 5).

Further, there is a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states, as well as drug or therapeutic response. However, the art is highly unpredictable with regard to the functionality of polymorphic sites in genomic DNA. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state, a physiological state, or drug metabolism or response. For example, Hacker et al. teaches that they were unable to confirm an association between a gene polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Hacker et al; Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the p-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 1998; 281 (5384):1787-1789). The unpredictability of the functionality or use of SNPs is not limited to diagnostic uses, but is found in therapeutic response as well. Malhotra et al (Am. J. Of Psychiatry, vol. 161, pages 780-796, May 2004) teaches that while a T102C polymorphisms in the serotonin 5-HT2A gene was reported to have a significant association with the failure to respond to clozapine in 149 patients with chronic schizophrenia, such effect was not able to be replicated in a series of subsequent studies (see page 7829 col 2). Malhotra et al teach that definitive studies in larger group sizes, prospective clinical data, and comprehensive analysis of

the gene will be needed to further address the role of this gene in antipsychotic drug response (see page 783, col. 1).

In the instant case, the specification only provides information that the T/C variant exists in humans and is associated with breast cancer, but provides no guidance that it has any effect whatsoever on the expression or activity of human MAPK10 or the broadly claimed sequences let alone any potential association with therapeutic effect.

The level of skill in the art:

The level of skill in the art is deemed to be high, however the experimentation required to practice the broadly claimed invention is even higher.

The quantity of experimentation necessary:

The quantity of experimentation in this area is extremely large as it requires analysis of each position in SEQ ID NO: 2, as well as the broadly encompassed mutants, variants, and homologs encompassed by claims 1, 53, 61 and 67, to determine whether any alteration at each position is associated with breast cancer or therapeutic response and to identify which variations are predictably associated with breast cancer in any subject. As neither the art nor the specification provide guidance as to which alterations at positions throughout MAPK10 or SEQ ID NO: 2 are predictably associated with breast cancer or therapeutic response, such analysis is replete with trial and error experimentation, with the outcome of each analysis being unpredictable. Screening each possible alteration in the broadly claimed genomic sequences, including SEQ ID NO: 2, as well as the mutants, variants, and homologs encompassed by the

claims, represents an inventive and unpredictable undertaking in itself, with each of the many intervening steps, not providing any guarantee of success.

In order to practice the invention as claimed, one would first have to establish that a predictive relationship exists between the disclosed polymorphisms and breast cancer or therapeutic response in any subject. Further, the scope of many of the claims requires knowledge of an association between all mutations in any MAPK10 gene and breast cancer or therapeutic response in humans or any species. Due to the scope of the claims, one of skill in the art would be required to further undertake extensive trial and error experimentation with a large number of patients with breast cancer, as well as patients undergoing different therapy, and controls, to determine mutations that share a predictive correlation with breast cancer or therapeutic response.

Thus, given the broad claims in an art whose nature is identified as unpredictable, the state of the prior art, the lack of guidance in the specification, the breadth of the claims and the quantity of experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention commensurate in scope with the claims.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 55 and 67-69 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 55, the term "e.g." in the parenthesis renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claims 67-69 are indefinite as it is unclear if the "two or more" polymorphic variations are at the same position or different positions. It is unclear if they refer to alternative alleles at a particular position, or to two different positions on a sequence. For example, in the whereby clause in claim 67, it is recited that "the presence of the polymorphic variation"... whereas the preamble is directed to "two or more". In claim 68, it is further unclear if the "two or more nucleotide sequences" are different copies of the same sequence, or fragments of the same sequences, that is one with a specific allele and one with the alternative allele, or to two entirely different sequences. In claim 69, the recitation of "wherein the two or more polymorphic variations are at one or more positions in wherein the one or more polymorphic variations are detected at one or more positions" is indefinite in that it is not clear if "two or more" or "one or more" is meant to be claimed. In response to the restriction requirement to elect one or a specific combination of positions, applicants only elected one position. Accordingly, the recitation of "two or more" is not understood in the context of the election with regard to these claims.

Conclusion

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-

0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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8/1/06